

Comments on Research Needs

by Norton Nelson*

I will not attempt to summarize all of the excellent work presented at this meeting—such a summarization would presume expertise in all of the varied fields which have been represented here, an expertise I do not possess. I believe it will be more useful for me to attempt a very personal assessment of those gaps which I see as now confronting us, in an attempt to identify those that are significant and merit attack. In short, “Where should we go from here?”

First, a general statement. I was charged with a similar task last August at a conference convened by FDA on work done on PCBs within the federal government. The extent of additional work that has surfaced as the result of the present conference is remarkable. Clearly, many universities and governmental agencies are extremely interested in the PCBs and have been working intensely in the field in the last few years. I will follow the order of presentation in the present conference roughly, but will assume the liberty of regrouping where this seems desirable.

Analysis

Analytical techniques have improved immensely in the last three to four years since the disturbing peaks resembling DDT metabolites were identified on chromatograph traces. It now appears that analytical procedures of considerable specificity are now available and quite widely used. The confusions and uncertainty of several years ago appear to have been largely mastered. The procedures are in some degrees overly tedious and have serious defects in respect to quantitation, especially because of the disparate response of some of the detector systems used in the gas

chromatographic analysis. The latter has made quantitation of mixed isomers difficult and somewhat uncertain. Clearly then, there is a need for improved quantitation in respect to mixed isomers and equally room for improved efficiency of the analytical techniques.

There is a very substantial gap in reliable analytical techniques for impurities such as the chlorinated dibenzofurans. It appears fairly definite that such impurities are present in some preparations and may indeed significantly account for some of the toxicity. Accordingly, better means for identification and measurement of these impurities is required. Because they occur only in the part per million range in the PCBs themselves, which in turn occur in the biosphere in the part per million range, extreme and perhaps unattainable sensitivity would be required for their identification in environmental samples. It may, however, be very important to make the attempt. A closer and more attainable goal would be the development of adequate techniques for detection and measurement of such impurities in the original PCBs themselves.

In this connection, it may be desirable to look for biological assays as at least an interim approach to this problem. Dr. Vos, in his excellent presentation, has presented work which suggests possibilities in the use of bioassays in the assessment of impurities in PCBs. This appears to be a very promising approach and should be pursued.

It is proposed below that selected purified isomers of the PCBs and their impurities be made available for toxicological studies. These would also be very useful in the further improvement of analytical techniques.

Environmental Transport, Distribution and Alteration

Dr. Sarofim and Dr. Nisbet, in their paper, and

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Dr. Risebrough, in his, have undertaken overall assessments of environmental sources, patterns of distribution and alteration of the PCBs. It has already been clear from earlier surveys reinforced by studies presented at this conference, that the PCBs are very widely distributed and are almost ubiquitous in their presence at many levels in the biosphere. It appears, however, that their distribution may be less uniformly global and more representative of local sources than DDT and its analogues. The approaches used in the two papers noted represent a very good beginning and serve to define, albeit perhaps only in an initial way, some of the major features in the overall PCB budget. Equally important, they serve to define gaps in our knowledge which may play decisive roles in developing a sound analysis of environmental distribution patterns. I note a series of items emerging as urgently needing clarification:

1. Further refinement of sources, including:
 - a. Patterns of marketing and use. Improvement here will require improved access to such information from producers and distributors.
 - b. Dumping practices.
 - c. Stability of semisequestered sources, e.g., capacitors in dumps.
2. Better quantitation of discharge amounts by route into water and air.
3. Appropriate analysis to determine the relative role of vapor versus particle borne PCB in aerial transport.
4. Rain out data in selected regions to assess the atmosphere as a transport route, by season and by region. Allied to this is the need for appropriate selective analyses of dated snow deposits for the development of time trends.
5. Clarification of the importance of localized as opposed to generalized sources of PCB. As only one example of the many dilemmas, the Sarofim-Nisbet scheme requires mid-ocean dumping to explain some high PCB values far at sea. Are such sources important?
6. Clarification of the role of particle bound as contrasted to dissolved PCB in water transport.
7. Development of a more efficient moni-

toring strategy as a means of optimizing analysis and the development of global distribution patterns of PCB's.

In approaching the global problem, one must not overlook the importance of more localized systems of contamination. Again a beginning towards this was illustrated in the paper of Dr. Veith. Studies of well defined localities can provide not only knowledge relevant to the specific units examined, but may permit extrapolation to other similar regions as components in the broader global scheme.

These presentations made very clear the serious gaps arising from our ignorance of environmental patterns of alteration of the PCB's and their contaminants. This was brought out in the excellent report of Dr. Hutzinger on photolysis of the PCB's. Work such as this needs to be extended, and, at an appropriate point in their development, brought into more realistic relationship to the form in which the PCB's are found in the atmospheric and aquatic environments, e.g., photolysis of PCB's as vapor, on particulates, and so forth. It is also very clear that attempts to deal with the transport and distribution problem are frustrated by lack of understanding of biological alteration of PCB's, that is, the metabolism of the PCB's by biological systems at all levels.

Occurrence

The insidious way in which PCB's have found their way into unexpected sources of exposure was illustrated by Dr. Kuratsune's report on carbonless copying paper. Although the statement has been made that substitutes for PCB's in carbonless copying paper have now been found, the completeness of this substitution will require monitoring. It may also be desirable to check body burdens of those routinely using forms with carbonless copying papers.

Similarly, the reports of Dr. Trout and Dr. Kolbye, on the presence of PCB in papers used in food packaging, further illustrate the need for vigilance for detecting and preventing the escape of these materials into unanticipated places. Although it appears that most of the major sources of PCB contamination in paper and cardboard have been identified and intercepted, this

optimism needs to be tempered by continuing scrutiny of food packaging material.

The reports of Dr. Kolbye and Dr. Berglund, on the presence of PCB's in foods, suggest considerable similarity in the general patterns of food contamination in Sweden and the U.S. In each instance, fish, particularly fresh water fish, appear to be the largest dietary source. Milk has been found heavily contaminated on occasion. Hopefully, this is no more than episodic, resulting chiefly from the contamination of silage from PCB's in silo lining paints as described by Dr. Fries. This mode of contamination clearly needs careful scrutiny and correction. Control will be simpler with major milk producers than with the smaller units, and particular attention should be given to the latter. In a related matter, the possibility that human milk may be a significant source of exposure of nursing infants needs further examination.

The data from FDA is perhaps heavily biased by including a large number of samples secured as part of compliance studies. A more orderly picture of PCB distribution in food will require a more systematic sampling pattern and this should be undertaken. Similarly, food surveillance is now hampered by inadequate techniques for detecting the presence of possible impurities in the PCB's. As noted above, resolution of this issue will require either chemical analytic techniques many orders of magnitude more sensitive than are now available or bio-assays as suggested above.

Animal Toxicology

The Biotest studies are now complete and were well summarized by Dr. Keplinger. A somewhat parallel study at Chamblee is still incomplete (personal communication, Dr. Renate Kimbrough). Examination of the complete data from the Biotest and the Chamblee work will be required before a full assessment of these toxicity studies can be made. Several issues present themselves. The extreme sensitivity of the mink, both in lethality (1), and in possible reproductive injury (2), raises an alert which will require resolution before we can take too much comfort from results showing lower toxicity in other mammals. Regrettably, this conference did not include an updated report on studies of mink. Although the Biotest report indicates no evidence for PCB

carcinogenicity, one (possibly two cases) of bladder cancer may have been identified in the Chamblee study (Personal communication, Dr. Renate Kimbrough). These findings will require that we await the completion of the Chamblee study and examine the Biotest reports in more detail before we can further clarify the question of malignancy.

Reproduction seems to be one of the most vulnerable functions in PCB poisoning. This is true in mammals as well as in other life forms, including both fish and birds. Again, the report on embryotoxicity in the rabbit (3) (not discussed here) suggests that this issue be further examined in mammals. It would also be desirable to relate reproductive effects to PCB burdens in wild populations.

It is a remarkable circumstance that despite the interest in the problem, the kinetics, distribution, metabolism and excretion of PCB in animals are only very scantily understood. There is some data on half time of body burdens in the fat in the cow (Fries) and in the rat (4) but the information is still quite inadequate. To jump ahead, it is unfortunate that such data did not emerge from study of the Yusho victims. These basic questions of metabolism, excretion and distribution need resolution and appropriate research should be put underway immediately.

The range of sensitivity to PCB is enormous, thus invertebrates show effects at levels of a few ppb (5). At the other extreme, *E. Coli* appear to thrive at thousands of ppm (Keil). Fish, birds and mammals fall between these extremes, with fish and birds appearing to be more sensitive than mammals. Again, reproduction appears to be the most vulnerable function. In respect to birds, and in contrast to DDT, it appears that hatchability may be more important than egg-shell thinning.

This area of comparative toxicity from species to species is so large and uncharted that generalities seem out of place. It would thus seem desirable for those involved in the study of interdependence within the biosphere to plan carefully the necessary studies to clarify these issues of comparative metabolic patterns by species. As suggested above, such studies may be of great consequence for determining overall patterns of transport and the ultimate fate of these materials in the environment.

A problem that persists in confusing our understanding of the toxicity of the PCB's is the unresolved question of contaminants and the different isomeric constituents of the various technical PCB's. This has led me to the strong conviction that it will be very desirable to select a modest number of representative isomers which should be synthesized and highly purified, and then carefully examined toxicologically. The selected isomers should be chosen on the basis of the best judgment available as being likely to typify not only "average" biological properties but also those corresponding to limiting or boundary biological actions in a qualitative as well as quantitative sense. Synthetic capabilities, we are told, are quite adequate to meet this challenge. Included in this should be well defined examples of the chlorinated dibenzofurans. Such an approach should permit a more rational planning of future toxicological work. These pure compounds will also be indispensable in the further development of selected bio-assays.

Mechanism of Action

Vos has described five distinctive patterns of pathologic outcome, acnegenic, liver damage, porphyria, edema and immunosuppression which he believes are differing contributed to by different chemical components in the crude PCB preparations. As just noted, the availability of purified trace contaminants and isomers would permit an extension and refinement of this important approach to an understanding of pathogenesis.

A number of studies have thrown light on some intracellular actions; however, it can hardly be said, at this stage, that we have good suggestions as to the major underlying mechanisms of toxicity. Rather than to hastily examine the effect of PCB's on a myriad of in vitro test systems, it would seem wiser that these studies be carefully planned as aids to understanding the observed course of PCB poisoning in the intact animal.

Human Body Burden

The reports from Dr. Yobs and Dr. Price and the comments from Dr. Hammer all point to the ubiquity of the presence of PCB's in humans in this country. PCB's occur in the fat of all segments

of the population and some gross features of population distribution have been identified. This work needs to be extended. In doing so, particular attention should be given to: 1) more representative population sampling, and 2) standardization on the basis of lipid content of the tissue. This latter appears to be especially important in relationship to plasma concentration. The lack of understanding of the kinetics of disappearance in humans hampers the interpretation of some of this data. Studies on primates could help clarify this issue.

Yusho

Dr. Kuratsune has presented us with a remarkable example of the quick rallying of medical and scientific talents to clarify the unfortunate accident leading to human PCB poisoning. The thorough and thoughtful studies of the staff of Kyushu University have provided excellent data on clinical effects and dose response in the Yusho episode. It is rare that such accidents have been so systematically studied. This data will necessarily play a major role in the assessment of the human hazard from the PCB's. We in this country should be deeply grateful for their skill and thoroughness in studying this episode. It would be extremely desirable to carry out detailed systematic, long term, follow-up studies, perhaps every five years throughout the life of the exposed individuals. We hope that their desire to make such follow-up studies for the assessment of possible chronic effects will be fulfilled. This country should be prepared to lend whatever collaboration it can in this very urgent matter.

General Comments

Extensive deposits of PCB's now exist throughout the biosphere. Even without further discharge, these deposits will remain for some years. It will be very urgent for us to develop information on distribution and degradation in order to reach some predictions as to the probable persistence of these deposits. The manufacturers of PCB in this country are now well alert to the problem and have announced a series of steps intended to restrict uses to those which are controllable. The success in achieving these reductions in usage will need monitoring. In addition,

however, the so-called "controlled" patterns of use, such as large scale transformers and capacitors, will in turn require monitoring against accidental discharge and leakage.

Substitution in the less controllable uses is apparently underway. It will be very important in carrying out such substitution, not to replace a known hazard with an untried, unknown, possibly greater hazard. Accordingly, considerable care in effecting substitution will be needed.

The approach used in the above discussions of concentrating on gaps—things not done as opposed to those which have been done—brings the risk of implying that our ignorance is greater than it actually is. The many detailed and solid papers presented at this conference and assembled here should serve as an adequate counterbalance against such misunderstanding. Nevertheless, our ignorance is still too large. I have thus tried to identify some places where, I believe, we need additional understanding. Finally, I apolo-

gize for the necessity forced upon me by the shortness of time, of omitting from these remarks discussion of a number of important contributions at this conference.

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